Paediatric endocrine protocol book

IMPORTANT

Endocrine tests with timed samples

If you are taking an endocrine test with timed samples you must have a separate HISS form for each sample.

The sample date and time must be correct. If you are not sure at which time you will be starting the test, you should give the basal (time 0) request a sample time of 0900h with proceeding samples timed from then. If you send multiple samples down with only one form, however clearly labelled, all the samples but one will be discarded.

If you are doing anything unusual it is best to discuss with the Duty Biochemist (ext. 8089) in advance.

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Endocrine protocol book

This book contains standard protocols for endocrine testing lists of the investigations available for some common endocrine problems and a list of paediatric endocrine drug doses.

Potential sources of advice:

Nicola Bridges (bleep 8687).

Dr Maggie Hancock (Chemical Pathology*)- discuss any unusual requests or complicated tests, particularly if results are going to be needed urgently .*

Penny Fletcher (Pharmacy, bleep 8492)- *for advice about drugs and doses.*

Endocrine stimulation tests

This section includes standard protocols for commonly used tests in paediatric endocrinology. I have included some references- not the original reference explaining how to do the test but recent updates on the value of the test or interpretation. There are notes concerning the potential risks of water deprivation tests and glucagon tests. It is important everyone doing the test is aware of these before the start.

Some of the drugs needed for stimulation tests must be ordered well in advance- discuss this with Penny Fletcher in Pharmacy.

Most of the protocols are taken from the GOS protocol book. Reference for this and a more complete list of tests-

MT Dattani: Tests in paediatric endocrinology and normal values. In: *Clinical paediatric endocrinology* editors CDG Brook, PC Hindmarsh (4th ed), Blackwell.

Fasting and start times for endocrine tests

Test	Fasted?	Start time important?
Water deprivation test	no	no
GnRH test	no	no
HCG test	no	no
Glucose tolerance test	yes	yes*
Standard short synacthen (= tetracosactride test)	no	yes*
Glucagon test	yes	yes*
TRH test	no	no

Fasting = nothing except plain water from midnight unless instructed otherwise

*start time is 9-9.30 am, so patients must be in well before this to allow for cannula, etc.

Standard short synacthen (tetracosactride, ACTH(1-24)) test

Indications

Suspected adrenal insufficiency (primary or secondary)
Investigation for enzyme defects in CAH and premature adrenarche
The test will detect significant suppression (eg with high dose steroids) but may not be suitable for looking for subtle effects (the modified synacthen test may be more suitable)
Tetracosactride is the new name for synacthen which is made up of the first 24 amino acids of the 36 in natural ACTH.

Precautions

Anaphylaxis to tetracosactride (synacthen) has been reported but is rare. The test should only be carried out in clinical areas with resuscitation equipment.

Preparation

Tetracosactride (synacthen) should be ordered at least 24 hours in advance.
The cannula should be inserted at least 1 hour before the test and the patient should rest on the bed during the test.
This test is usually performed at 0900hr, although exact timing is not vital.
Fasting is not required.
Omit the morning dose of hydrocortisone if the child is taking it (and give it when the test is over). If the child is on any other steroid medication, discuss in advance.

Protocol

Dose of tetracosactride (synacthen):
For neonates and preterm infants dose by weight is 36 micrograms/kg
Under 6 months: 62.5 micrograms
6-24 months: 125 micrograms
Over 24 months: 250 micrograms
Give iv and flush in well with 0.9% saline.

Samples:
Baseline (0 mins) before the tetracosactride (synacthen), then at 30 and 60 minutes.
Investigation of adrenal insufficiency- cortisol
Investigation of CAH-cortisol and 17 hydroxyprogesterone

Other bloods:
If ACTH assay is needed, this must be taken before the test. The sample needs to be taken into a plastic EDTA tube. Microtainer EDTA tubes are

acceptable- 3 of these should be filled to the 600 microlitre mark and taken to the laboratory on ice.

For potential adrenal insufficiency, take electrolytes and glucose levels. Give any steroid replacement before the child goes home.

Results
Normal response is a peak of over 550mmol/l or an increment of 200mmol/l.
The 17 hydroxyprogesterone peak is increased in 21 hydroxylase defects. Refer to a standard chart .

References
Gonzálbez, , Villabona, , Ramón, , Navarro, , Giménez, , Ricart, & Soler, Establishment of reference values for standard dose short synacthen test (250µg low dose short synacthen test (1 microgram) and insulin tolerance test for assessment of the hypothalamo-pituitary-adrenal axis in normal subjects. *Clinical Endocrinology* 53 (2), 199-204.

New MI, Wilson RC. Steroid disorders in children: congenital adrenal hyperplasia and apparent mineralocorticoid excess. *Proc Natl Acad Sci USA* 1999; 96: 12790- 12797.

Modified or physiological synacthen (tetracosactride) test

Indications
The standard tetracosactride (synacthen) test gives a supraphysiological dose of tetracosactride (synacthen) and will not detect subtle degrees of adrenal insufficiency. Much lower doses may give greater sensitivity. This test may be of diagnostic value if adrenal insufficiency is suspected but standard test is normal. A standard dose of 1 microgram is often used in adults.

Precautions
Anaphylaxis to tetracosactride (synacthen) has been reported but is rare, and very unlikely with low dose tests. The test should only be carried out in clinical areas with resuscitation equipment.

Preparation
Fasting is not required.
Order the tetracosactride (synacthen) from pharmacy at least 24 hours in advance.
iv cannula should be inserted at least 3 hours before the start of the test.
The patient should rest on their bed for 2 hours before, and during the test.
The test must start at 2.00pm- timing is important to coincide with the normal fall in cortisol during the afternoon.

Protocol
Prepare the diluted tetracosactride (synacthen)
Add 250 micrograms of tetracosactride (synacthen) to a 1 litre bag of 0.9% sodium chloride and shake well. The resulting solution is 250 nanograms per ml.
Dose is 500 nanograms per 1.73m^2 body surface area, (=2ml of the diluted solution per 1.73m^2 body surface area).

$$\text{Body surface area} = \sqrt{\frac{\text{Height (cm)} \times \text{weight (kg)}}{3600}}$$

-or use the nomogram in the Guy's formulary.

Give the dose iv and flush well with saline.
Take blood for cortisol before the tetracosactride (synacthen) and then at 10, 15, 20, 25, 30, 35, 40, 45 minutes after.

Results

Normal response is a peak of more than 550mmol/l cortisol or a rise of over 200mmol/l.

References

González, , Villabona, , Ramón, , Navarro, , Giménez, , Ricart, & Soler, Establishment of reference values for standard dose short synacthen test (250 micrograms) low dose short synacthen test (1 microgram) and insulin tolerance test for assessment of the hypothalamo-pituitary-adrenal axis in normal subjects. *Clinical Endocrinology* 53 (2), 199-204.

Agwu JC. Spoudeas H. Hindmarsh PC. Pringle PJ. Brook CG. Tests of adrenal insufficiency *Archives of Disease in Childhood.* 80(4):330-3, 1999.

Prolonged synacthen (tetracosactride) test

Indications
Investigation of adrenal insufficiency- if there is hypothalamo pituitary disease the adrenal glands will be atrophied but may respond to a prolonged stimulus.

Precautions
Sensitivity to tetracosactride (synacthen) has been reported.
Remember that tetracosactride (synacthen) depot is not the same as the synacthen used for the short synacthen test.

Preparation
Order the tetracosactride (synacthen) depot from pharmacy at least 24 hours in advance.
Make a plan for the injections- a good way to do this is to give the first one on the ward, give the next 2 doses to the family and then contact the GP practice to give the injections. Do not ask the GP to prescribe the depot synacthen or to take the end of test sample since this is likely to go wrong.

Protocol
Take baseline sample for cortisol at 9.00am on day 1

Dose of tetracosactride (synacthen) depot
Under 6 months 250 micrograms
6-24 months 500 micrograms
over 2 years 1mg

Give this dose as an im injection, at 9.00am on days 1, 2, 3.

Take blood for cortisol 4-6 hours after the last injection on day 3.

Results
Plasma cortisol should rise more than threefold or by over 200nmol/l.
Failure to respond suggests primary adrenal disease.

Oral glucose tolerance test

Indications

This test is not indicated in the assessment of type 1 diabetes.

Investigation of potential insulin resistance or impaired glucose tolerance (children with severe obesity, acanthosis nigricans, polycystic ovarian disease, strong family history of type 2 diabetes).
Investigation of hypoglycaemia- looking for rebound hypoglycaemia.
Tall stature- to look for abnormal GH secretion in pituitary gigantism.

Precautions

Do not do this test if blood glucose measurements have already confirmed diabetes- ie a random blood glucose over 11.1 mmol/l.
In a child with diabetes the large glucose load will result in high glucoses which may precipitate DKA.
There is a risk of rebound hypoglycaemia. This is most significant in those with hyperinsulinism or recurrent hypoglycaemia.
Some children find the glucose difficult to drink, or may vomit.

Preparation

The child should be fasted from midnight. Drinks of water are allowed.
The test should start at 9.00-9.30 am.
Work out the glucose load and order from pharmacy at least 24 hours in advance. This can be given as a glucose drink (eg fortical) or as glucose powder dissolved in squash.

Protocol

Dose of glucose
1.75 g/kg glucose to a maximum of 75 g.

Samples
Take blood at 0 mins and give the glucose drink
Take bloods at 30, 60, 90, 120 and 180 minutes after the drink.
Take blood for glucose and check glucose on a ward based machine for each sample.

Investigation of potential insulin resistance or impaired glucose tolerance: samples for insulin may be indicated (discuss).
Tall stature: GH
Hypoglycaemia: other samples will be required if the child becomes hypoglycaemic (see under investigation of hypoglycaemia).

Make sure that the child has eaten lunch and kept it down before leaving ward. Keep the cannula in until then because of the risk of rebound hypoglycaemia.

Results

WHO guidelines, 2000

Plasma glucose mmol/l	*Fasting*	*2 hours after glucose load*
Diabetes mellitus	Over 7	Over 11.1
Impaired glucose tolerance		7.8-11
Normal	under 6.1	Under 7.8
Impaired fasting glucose	6.1-7	

Insulin resistance- elevated baseline insulin and/or exaggerated peak insulin response. There are a number of mathematical ways of looking at this.

Tall stature: GH should suppress to baseline at 30-60 minutes

Human Chorionic Gonadotrophin (HCG) test

Indications

To asses the ability of the testes to secrete testosterone (suspected anorchia, anatomical or developmental defects of the testes, enzyme defects, following torsion).
In infants with normal testicular function there may be spontaneous testosterone secretion (testosterone concentrations 10-30nmol/l).
Under 6 months of age, a random sample (for testosterone, LH, FSH) should be obtained. This may confirm the situation and avoid an HCG test.
(Investigation of possible 5α reductase deficiency- very rare).

Precautions

You must do a GnRH test before the HCG test (or over 6 weeks after) if you are planning one. HCG has a very long half life.
There are no contraindications.
In boys with normal testes there may be some virilisation (increase in testicular size, erections).

Preparation

Order the HCG from pharmacy at least 24 hours in advance.
Make a plan for the injections- a good way to do this is to give the first one on the ward, give the next 2 doses of HCG to the family and contact the GP practice to give the injections. Do not ask the GP to prescribe the HCG or to take the end of test sample since this is likely to go wrong.

Protocol

Dose of HCG (IM injection)
under 1 year 500 units
1-10 years 1000 units
over 10 years 1500 units

Give HCG as an im injection on Monday, Wednesday and Friday.

Sampling
Baseline bloods: testosterone , LH, FSH, karyotype* if not done before
On the Monday after the third injection: testoterone
Other similar time plans can be used for the tests and injections.

(Investigation of possible 5α reductase deficiency: take dihydrotestoterone levels at start and finish of the test. A separate sample is needed. Type DHT to find on Lastword.)

Results

** Karyotype- minimum 2ml Lithium Heparin blood, with a Kennedy Galton Centre request form. Must be sent to the lab before 1200hr.*

Testosterone levels should rise by 2 to 3 fold. Poor or absent response, particularly with elevated FSH and LH at the start of the test, indicates impaired testicular function (or no testicular tissue). Individuals with hypogonadotrophic hypogonadism (ie pituitary or hypothalamic problem) may have a normal response.
Investigation of possible 5α reductase deficiency: the testoterone: DHT ratio is abnormal.

References

Davenport M. Brain C. Vandenberg C. Zappala S. Duffy P. Ransley PG. Grant D. The use of the hCG stimulation test in the endocrine evaluation of cryptorchidism. British Journal of *Urology.* 76(6):790-4, 1995 Dec.

Water Deprivation Test

Indications
Suspected diagnosis of diabetes insipidus- differentiation from psychogenic water drinking.
The administration of desmopressin (DDAVP) can distinguish nephrogenic from central DI.

Precautions
This test carries significant risks if the child actually has DI. Withholding fluids from a child with DI will result in severe dehydration. Do not start the test if the diagnosis is already made, and stop as soon as you get a diagnostic sample (which is why bloods need to be done urgently). Careful monitoring is vital while the test is continued and free access to fluids must be given until the start of the test (no overnight fast).

Administration of desmopressin (DDAVP) carries the risk of water overload if the child is allowed to drink freely. Intake should be limited to the replacement of losses during the test.

Preparation
Obtain a number of paired plasma and serum osmolality measurements before performing a formal test- this may confirm DI or normality and avoid the test. Urine osmolality of over 750 mosm at any time excludes DI.

Cortisol deficiency will interfere with the ability to excrete water and may mask DI- exclude cortisol deficiency before this test in any patient at risk.

Speak to the Duty Biochemist (ext 8089) a few days before the test to check that the samples can be done urgently. Phone again when you are about to start the test.

Obtain the desmopressin (DDAVP) from Pharmacy at least 24 hours in advance.
Weigh the child and calculate 5% of the weight.
Arrange for suitable nursing support to supervise the child and perform observations. Accurate record keeping is essential, particularly if desmopressin (DDAVP) is given as part of the test.

Do not fast or restrict fluids overnight.
Start at 8.30-9.00 to reduce requirement for bloods to be sent out of hours.

Protocol

Baseline

Put in an iv cannula.

In younger children, stick on a urine bag (use the kind of bag that can be emptied without unsticking it). Obtain a urine sample if possible and send for osmolality.

Take blood for electrolytes and osmolality.

Start fluid fast.

Observations

Check weight, pulse, blood pressure every hour.

Record time and volume of urine, sending each sample for osmolality. If possible, ask the child to void hourly or just before the blood samples.

Take blood for electrolytes and osmolality every 2 hours.

Stop the test

- If urine osmolality exceeds 750 mOsm. This excludes DI and you do not need to give desmopressin (DDAVP).
-

Stop the test and give desmopressin (DDAVP)

- If plasma osmolality rises above the normal range (over 295 mOsm) or sodium is elevated (over 145mmol/l) with an inappropriately dilute urine (under 300 mOsm).
- If the weight falls by more than 5% or the child becomes clinically dehydrated.

If you have already reached the end of the day it may be sensible to defer the trial of desmopressin (DDAVP) until another day. Infants should be restricted for no more than 6-8 hours, older children may need longer.

desmopressin (DDAVP) im dose:
Under 2 years old- 0.1 micrograms
2-8 years- 0.2 micrograms
8-14 years 0.3 micrograms
over 14 years 0.4 micrograms

or desmopressin (DDAVP) can be given nasally, as intranasal solution or as metered dose spray. The dose needed is different and must be discussed in advance. Do not underestimate the difficulty of administering nasal drugs to a struggling toddler when deciding which route to use. Desmopressin (DDAVP) tablets are not suitable.

After desmopressin (DDAVP)

Food is permitted but fluid should be limited to the volume of urine passed in the previous hour. Measure urine volume and send each sample for osmolality. The test can be stopped if urine osmolality exceeds 750 mOsm. Check electrolytes at the end of the test and monitor intake until

the desmopressin (DDAVP) wears off. If the urine osmolality remains low this suggests nephrogenic DI- continue monitoring input and output for 4-6 hours after the desmopressin dose.

Results

Interpretation of a water deprivation test

Urine osmolality (mOsm)

After fluid deprivation	after desmopressin (DDAVP)	diagnosis
< 300	> 750	Nephrogenic diabetes insipidus
<300	<300	Cranial diabetes insipidus
>750	>750	Normal
300-750	<750	?partial nephrogenic DI ?psychogenic water drinking
300-750	>750	?partial cranial DI

Elevated serum osmolality with inappropriately dilute urine confirms DI.

References

Diederich S. Eckmanns T. Exner P. Al-Saadi N. Bahr V. Oelkers W. Differential diagnosis of polyuric/polydipsic syndromes with the aid of urinary vasopressin measurement in adults. *Clinical Endocrinology.* 54(5):665-71, 2001 May.

GnRH (gonadorelin) test

Indications
GnRH (gonadorelin, LHRH) will stimulate LH and FSH secretion from the normal pituitary in a child of any age. Higher response is seen in puberty. Test may be of value in the investigation of sexual precocity or suspected hypogonadotrophic hypogonadism.

Precautions
Order the GnRH (gonadorelin) in advance. Pharmacy need 1-2 weeks notice because this drug is not held in stock and supplies are difficult.

Preparation There is no need to fast and time is not important. LH, FSH, oestradiol/testosterone assay needs 2 full microtainers.

Protocol
Baseline
Take blood for LH, FSH, oestradiol/testosterone and karyotype* if needed.

Dose of GnRH (gonadorelin)
2.5 micrograms /kg to a maximum of 100 micrograms
Give as iv bolus

Measure LH and FSH at 30minutes and 60 minutes.

Results
- LH and FSH responses rise during normal puberty (and also precocious puberty)
- In gonadal failure the response is exaggerated
- In gonadotrophin independent precocious puberty the LH and FSH response is suppressed.
- The test will not definitely distinguish pubertal delay from hypogonadotrophic hypogonadism.

References
K Ghai, JF Cara, and RL Rosenfield Gonadotropin releasing hormone agonist (nafarelin) test to differentiate gonadotropin deficiency from constitutionally delayed puberty in teen-age boys--a clinical research center study *J. Clin. Endocrinol. Metab*. 1995 80: 2980-2986.

** Karyotype- minimum 2ml Lithium Heparin blood, with a Kennedy Galton Centre request form. Must be sent to the lab before 1200hr.*

Glucagon test (of the hypothalamic pituitary axis)

Indications

Stimulation test for suspected GH insufficiency
The test can be combined with TRH and GnRH tests
Patients who are immediately pre puberty or have delayed puberty should have treatment with sex steroids before the test ("priming").

Precautions

Contraindications:

- Suspected phaeochromocytoma or insulinoma
- poorly controlled fits
- untreated adrenal insufficiency
- glycogen storage disease

The test is unreliable in diabetes.

Important

The risks associated with glucagon stimulation tests

Glucagon results in delayed hypoglycaemia. The hypoglycaemia may be the reason for the stimulus to GH secretion. The risks associated with glucagon tests (and insulin stimulation tests) are associated with this hypoglycaemia, and most of the problems have arisen after excessive glucose administration after hypoglycaemia. This is a safe test if the staff involved are aware of the potential problems and you are well prepared.

The rules for glucagon tests

- Only do one when Nicola Bridges and registrar are here
- A doctor must be present with the patient throughout the test and not leave the ward.
- Patient must be "specialled" and the nurse should do bedside glucose monitoring-needs arranging in advance
- Don't do one without venous access
- Have glucose ready to give (see below). Carry on with the sampling even if you give this, the test is still valid.

Preparation Write up the glucagon beforehand and make sure it is on the ward. Glucagon is usually held as ward stock in the fridge.
Patient should be fasted (only water from midnight). If the patient is on hydrocortisone replacement, omit the morning dose and give an iv dose after the test (see below).

Protocol
Insert an intravenous line and then allow the patient to rest for 30 minutes.
Take baseline bloods: FBC, U&E, Bone, LFT, Free T4, TSH, FSH and LH karyotype* (in girls) if it has not been done before.
Dose of glucagon:
100 micrograms per kg to a maximum of 1mg i.m.

Sampling

Time minutes	**ward blood glucose**	**lab glucose**	**GH**	**cortisol**
-30 (or with cannula)	4	4	4	4
0	4	4	4	4
30	4	4	4	
60	4	4	4	
90	4	4	4	
120	4	4	4	4
150	4	4	4	4
180	4	4	4	4

Management of hypoglycaemia (usually at 90-120 minutes)
- if glucose <2.6 mmols/L, then give glucose drink. Also if the child shows signs of hypoglycaemia, that is sweaty and drowsy, a glucose drink should also be given. Carry on with the test. If the child does not tolerate oral glucose give iv treatment.

- Give glucose intravenously -10% dextrose, 2 mls/kg (200 mg/kg) over 3 minutes.

** Karyotype- minimum 2ml Lithium Heparin blood, with a Kennedy Galton Centre request form. Must be sent to the lab before 1200hr.*

- Continue with the glucose infusion intravenously using 5% dextrose at 0.2ml/kg/min.

- Remeasure glucose concentration after 4 to 5 minutes. Adjust glucose infusion to maintain the blood glucose at 5 - 8 mmols/L.

- Do not give intramuscular injections of glucagon unless venous access is lost.

- If hypopituitarism is suspected, 100 mg of hydrocortisone can be administered intravenously.

Procedure at the end of test

The child should not be sent home until an adequate meal has been taken. The intravenous cannula should be left in situ until lunch has been completed. Give 100mg iv hydrocortisone at the end of the test if the child is on replacement or is at risk of adrenal insufficiency.

Results

A normal GH peak is over 20mU/l, cortisol should rise to over 550nmol/l (or an increment of over 200nmol/l).

References

Dattani M, Hindmarsh PC, Pringle PJ, Brook CGD. What is a normal stimulated GH concentration? *J Endocrinol* 1992; 133:447-50.

Shah A, Stanhope R, Matthews D. Hazards of pharmacological tests of growth hormone secretion in childhood. *Brit Med J* 1992; 304:173-4.

Ghigo E, Bartolotta E, Imperiale E et al. Glucagon stimulates GH secretion after intramuscular but not intravenous administration. Evidence against the assumption that glucagon per se has a GH releasing activity. *J Endocrinol Invest* 1994; 17:849-54.

Thyrotropin releasing hormone test, TRH (protirelin)test

Indications
Not commonly required but may be included in pituitary function testing with glucagon and GnRH test.
Evaluation of pituitary disease
Confirming a diagnosis of hyperthyroidism (if required)
In pituitary gigantism there is a GH response to TRH (protirelin).

Precautions
Significant reactions to TRH (protirelin) are rare. The test should only be carried out in clinical areas with resuscitation equipment. However nausea, odd tastes in the mouth, flushing, headaches, abdominal and chest discomfort are common, usually at the time of the injection. Caution is required in children with asthma.

Preparation
No fasting is required.
Order the TRH (protirelin) from pharmacy at least 24 hours in advance.

Protocol
The test can be done in conjunction with other pituitary function testing.
Baseline bloods: TSH, thyroxine. If indicated free T3, prolactin, GH.

Dose of TRH (protirelin).
7 micrograms/kg to a maximum of 200 micrograms
-give iv and flush in well with 0.9% saline.

Sampling
Bloods for TSH at 20 and 60 minutes after TRH.
GH and prolactin if indicated.

Thyroid function tests take a full 600 microliter microtainer. Prolactin and GH would need a further microtainer each.

Results
Normal response is an increment in TSH of 3-18mU/l (over 2 times the baseline).

Investigations in common endocrine conditions

The lists below are to assist in requesting appropriate initial investigations in some common endocrine problems. I have provided comprehensive list of all the tests you might consider and their value. It is definitely not my suggestion that you need to do all these investigations, neither do you have to do all the investigations before talking to me. I have listed some because I do not think you should do them.

It is a good rule never to order tests when you will not know how to interpret the results. I am happy to discuss patients at any stage. Some endocrine tests are very expensive and the lab will not do them unless discussed with me.

Nicola Bridges
January 2002

Problem: **Rickets**
Extensive investigations are not required for obvious nutritional rickets. The response to Vitamin D treatment is an important part of the assessment.

Wrist x ray
The appearances at X ray are characteristic- if the X ray shows rickets, this is the diagnosis. Resolution is very slow, there is no point in repeating the X ray after less than 3 months.

Bone profile
Ca may be low in rickets of any cause.

Electrolytes, creatinine
Exclude obvious renal problems

Alkaline phosphatase, liver function tests
Alkaline phosphatase will be elevated in all types of rickets. Falling Alkaline phosphatase is the best marker of healing rickets.

PTH
25 hydroxyvitamin D
PTH is likely to be elevated while 25 hydroxyvitamin D may not be very low. Neither test will accurately distinguish nutritional rickets from other causes at presentation. You do not need to do them in uncomplicated nutritional rickets.

Urine amino acids
Rickets elevates the PTH which results in aminoaciduria (whatever the cause)

Urine / blood pH
If there is suspicion of renal tubular acidosis

Urine / plasma phosphate, calcium and creatinine
There are nomograms for calculating tubular resorption of phosphate, the lab can calculate it or do it yourself:

$$\%TRP = [1-(U_{phosphate}/P_{phosphate})/ (U_{creatinine}/P_{creatinine})] \times 100$$

-where all phosphate measurements are in mmol/l, all creatinine in micromol/l.
Beware-urine creatinine is reported in mmol/l.

TRP is abnormal in hypophosphataemic rickets. Remember to check all the urine and plasma tests you need, at the same time.

Problem: suspected thyroid disease

Hypothyroidism, goitre, hyperthyroidism

TSH, free t4

In hypothyroidism, TSH is high and thyroxine low and in hyperthyroidism TSH low and thyroxine high. If you get one without the other it is unlikely to represent true thyroid disease.

Microsomal and peroxisomal antibodies

-in hypothyroidism

Anti TSH receptor antibodies

-in hyperthyroidism

Free t3

May be helpful in assessing hyperthyroidism but not needed as a routine test.

Ultrasound scan of the thyroid

Will examine the texture of a goitre (ie nodular or not), and tell a cyst from a nodule.

I^{131} scan of the thyroid

Needed to look at any thyroid nodules or lumps. Hot or cold nodules in children must be followed up (there is a significant risk of malignancy) and biopsy or removal considered.

Problem:obesity

Only do tests if you think they will help. Identifying risk factors is likely to be of more value than looking for a hormonal "cause" for obesity.

Thyroid function
Hypothyroidism rarely causes obesity although this remains a "standard" test.

Serum lipids
If there is a family history of heart disease.

Fasting glucose
Oral GTT
If the child has acanthosis nigricans you must at least do a fasting glucose. If there is a family history of type 2 diabetes or the child is very obese consider an oral glucose tolerance test.

24 urinary free cortisol
Initial test for suspected Cushing disease. "Typical" Cushings habitus and purple striae are quite common in normal, obese adolescents.

LH, FSH, testosterone, SHBG
Pelvic ultrasound
There is a relationship between obesity and polycystic ovarian disease. This is a group who can be offered effective treatment, so consider these tests in girls with irregular periods or amenorrhea, hirsutism, greasy skin, acne.

Karyotype looking for Prader Willi syndrome
Children with Prader Willi have a history of neonatal hypotonia and a characteristic eating pattern. They are also developmentally delayed, so it is not worth testing children who are clearly intellectually normal.

Leptin levels
MRI brain
Leptin levels can be measured as a research tool but not as a routine test. Very rare causes of obesity should be considered in those with eating habits and weight problems that are a long way out of the ordinary, and only when other areas have been explored. (These causes include hypothalamic tumours, leptin and melanocortin abnormalities).

Problem: short stature

Short and normally growing children may not need further investigations apart from accurate measurement and plotting. Check that the height velocity is normal over a reasonable period of time (usually at least a year).

Bone age

Bone age is a measure of the space left before growth ceases. Bone age is of little value in children under 3.

Calculate parental target height

People can be very inaccurate in estimating height so measure parents if required. This is definitely not a "height prediction" (so don't tell the parents that) but a rough assessment of genetic contribution to height.

karyotype*

The features of Turner syndrome can be very subtle- consider this test in any short girl, particularly if she is short for her parents.

FBC ESR
Coeliac set
B12, folate
Serum iron, ferritin

The pick up of coeliac disease and other gastrointestinal problems in short children is extremely low- excluding this as a cause may be of value.

Thyroid function

Once again the pickup is very low but do this if other bloods are being taken

Random or post exercise GH assay

A total waste of time

IGF 1, IGFBP3, LFTs

A marker of GH action- may be helpful if GH deficiency seems likely

Skeletal survey

Consider a skeletal dysplasia if the child is disproportionate. You need the right views and films should be reported by an expert - discuss with Dr Phelan.

Glucagon stimulation test

See under Glucagon test, above.

** Karyotype- minimum 2ml Lithium Heparin blood, with a Kennedy Galton Centre request form. Must be sent to the lab before 1200hr.*

Problem: hypoglycaemia

This is a very long list and the tests to do depend on the circumstances and the age of the child.
There is a separate protocol on the neonatal unit.

Important

- Hypoglycaemia is potentially damaging and no child should be left hypoglycaemic while you sort out tests.
- An expert opinion should be sought very early for metabolic disease or severe hyperinsulinism ("nesidioblastosis") because of the neurological consequences.
- Never use 50% glucose solution.
- Treat hypoglycaemia with a slow iv bolus (in term and preterm neonates, 2ml/kg of 10% glucose, in infants over 1 month 5-10ml/kg of10% glucose) followed by an infusion.

Glucose, electrolytes

Always confirm the hypoglycaemia with a lab glucose.

FBC, PCV

In newborns

Liver function tests

Marker of metabolic disease or liver pathology

Serum bicarbonate or pH
Ammonia
Lactate
Urine organic acid
Urine amino acids
Plasma amino acids
Urine reducing substances
Carnitine (free and acyl)

Markers of potential metabolic disease. This is more likely in the neonatal period. Several types of defect can present with hypoglycaemia (mitochondrial disorders, amino acid and organic acid defects, fatty acid oxidation defects, etc). Tests are more likely to be diagnostic if taken at the time- make sure the urine immediately after the episode is collected. Metabolic disease can also present in older children (eg fatty acid oxidation defects).

Calculate the glucose infusion rate

Glucose infusion rate (mg/kg/min) =

$$\frac{\text{Rate (ml/hr)} \times \text{concentration of glucose used (\%)}}{6 \times \text{weight (kg)}}$$

Rates of 15-22 mg/kg/min are often needed in hyperinsulinism. Normal infants need 4-6mg/kg/min.

Insulin†, C peptide, glucose
Always take a glucose at the same time. Insulin secretion should be suppressed during hypoglycaemia. Insulin has a very short half life and it can be hard to get a diagnostic test even in obvious hyperinsulinism. C peptide may be helpful because of a longer half life.

Serum cortisol
ACTH
GH
Synacthen test
Low cortisol in neonates is usually related to hypopituitarism. Adrenal disease is more likely in older children.

FFA's and b hydroxbutyrate
Urine ketones
Ketone production will be low in hyperinsulinism.

Toxicology, blood alcohol
Anyone in the house with type 2 diabetes?

† *insulin samples must come to the lab on ice for prompt separation.*

Problem: hypocalcaemia

Bone set
PTH levels.
Magnesium
Liver function tests
Electrolytes
Always confirm a "one off" low calcium with a repeat sample also check the serum albumin and electrolytes. Check magnesium, which can affect PTH levels.

Wrist X ray
The most common cause is nutritional rickets.

Serum PTH and calcium
PTH will rise in hypocalcaemia.

25 hydroxyvitamin D
This is not always low in rickets.

Urine / plasma phosphate, calcium and creatinine
If you are measuring urine electrolytes, ask for all of these -calculation of calcium to creatinine or tubular resorbtion of phosphate

Problem: suspected adrenal disease

Random serum cortisol
Diurnal rhythmn of cortisol
Very high or low random levels may be a good guide but diurnal rhythm is more helpful.

24 hour urine free cortisol
Screening test for Cushing's- there is an equation to allow for the size of the child. Can be normal in "cyclical" Cushing's.

Synacthen test
See under synacthen test

Adrenal androgens- DHEAS, androstenedione
If adrenal tumour is suspected- but one off levels will not always be high.

Renin, aldosterone
Renin will be elevated and aldosterone low if there is mineralocorticoid deficiency. Samples should go to the lab at once for separation, but not on ice. Take electrolytes at the same time.

17 hydroxyprogesterone
Suspected CAH in neonates- discuss with the lab who may be able to process early. Do not wait for results before treating. Refer at once.
Older children: 17OHP is not a first line investigation in premature adrenarche or hirsutism. One off values may not be of help in late onset CAH.

Urine steroid profile ‡
This is unlikely to be normal if there is an adrenal tumour secreting steroids. It may be of value in suspected enzyme defects but is not always abnormal.

Dexamethasone suppression test
There are a series of tests using different doses of dexamethasone. Overnight suppression test would be an initial test for Cushing's. In summary a low dose will suppress normal ACTH and cortisol secretion but successively higher doses are needed to suppress a pituitary adenoma and an adrenal tumour.

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‡ *Urine steroid profile is an expensive test and the lab will only do this after discussion with Nicola Bridges. If you think one might be required you can ask the lab to store the urine until you know.*

ACTH
Discuss with the lab before taking this. Very high ACTH with low cortisol suggests adrenal disease.

Bone age
Will be advanced if there are high levels of adrenal androgens .

Bone mineral density
Osteoporosis is a significant side effect of long term steroid medication.

Ultrasound of adrenal glands
This has limited value- there is no role for adrenal ultrasound as an initial screening test in suspected endocrine diseases. Define the situation first and then ask for MRI or CT if required.

MRI/CT of adrenal glands
See above

Problem: hypertension

Electrolytes
May be abnormal in renal disease or endocrine causes.

Renin and aldosterone
Renin will be high in renal artery stenosis (and a lot of other things). Most endocrine causes of hypertension have elevated aldosterone. Samples should go to the lab at once for separation, but not on ice. Take electrolytes at the same time.

Urinalysis
Calcium, uric acid
Renal ultrasound
Look for renal disease (or its causes).

Cholesterol
Cardiac risk factor

Echo, cardiac opinion
Looking for ventricular hypertrophy, coarctation etc.

Urine catecholamines
Discuss with the lab (neuroblastoma, phaeochromocytoma)

Urine steroid profile ‡
Will reach a diagnosis in some endocrine causes of hypertension. Should be considered only when other investigations indicate an endocrine cause for the hypertension.

24 hour tape for blood pressure
Can be helpful in determining the degree of hypertension. Needs to arranged with the adult physicians and obviously only on older children.

Renal arteriography (contrast or MRI)
For renal artery stenosis- other renal imaging may be of help before this so discuss with the department.

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‡ *Urine steroid profile is an expensive test and the lab will only do this after discussion with Nicola Bridges. If you think one might be required you can ask the lab to store the urine until you know.*

APPENDIX 1

Paediatric endocrine prescriptions
Most of these prescriptions will only be initiated in the endocrine clinic, by myself. This guide is to allow you to check that doses are correct.

Induction of puberty

For Turner syndrome, gonadal failure or pubertal delay
Treatment is started and then reassessed after 3-6 months. Most subjects will only need a short period of treatment before their endogenous puberty starts. If treatment is given to go through puberty the aim is to gradually increase over 2-3 years.

boys
initial treatment:
50mg testosterone esters (as Sustanon given by deep im injection) every 4 to 6 weeks
continue in 6 month steps- 50 mg every 4 weeks, then 100 mg every 4 weeks, then 100mg every 3 weeks and then 100mg every 2 weeks

girls
2- 5 micrograms of ethinyloestradiol daily
continue in 6 month steps-
ethinyloestradiol 5 micrograms, then 10 micrograms, then 15 micrograms, and then 20 micrograms daily
A progestogen should be added in when 15 micrograms ethinyloestradiol dose is reached, if there is a vaginal bleed, or endometrium thicker than 5mm on ultrasound (giving ethinyloestradiol from days 1 to 21 of a 28 day cycle 30 micrograms of levonorgestrel (Microval) for days 14-21).
Norethisterone 5mg can be used instead of the levonorgestrel but is associated with hirsutism.

Sex steroid maintenance

Males
100- 250mg Sustanon given by deep im injection every 2 weeks

Females
Ethinyloestradiol 20 micrograms in cycles as above or low dose oral contraceptive pill.

Oxandrolone

To accelerate pubertal growth spurt in pubertal delay- most effective for those with some sign of puberty already. 2.5mg daily oral for 3 months. Can be repeated once without advancing the bone age.
In Turner syndrome to accelerate growth
1.25mg daily.

Oxandrolone is available on a named patient basis, and takes a few days to order. Give pharmacy the patient's phone number so they can contact them when it is in.

PCO

Treatment to suppress ovarian androgen secretion:

20 or 30 micrograms ethinyl oestradiol daily from days 1 to 21 of a 28 day cycle and cyproterone acetate* 50mg daily from days 7-14
then
20 or 30 micrograms ethinyl oestradiol daily from days 1 to 21 of a 28 day cycle and cyproterone acetate* 25mg daily from days 7-14
then:
change to Dianette

Precocious puberty

GnRH analogue as 3.75mg leuprorelin (Prostap SR) monthly. Cyproterone acetate 100mg/m^2 orally for the first 4-6 weeks to suppress the initial "flare", then stop. Prostap 3 has been used but needs monitoring of suppression. If GnRH analogue not appropriate, cyproterone acetate* 100mg/m^2 daily.

Hypothyroidism

Give thyroxine if possible as crushed tablets -suspensions can be unreliable.

Congenital hypothyroidism

25 micrograms daily (for large infants start at 37.5 micrograms) daily.as crushed tablets- aim is to produce rapid suppression of TSH with free T4 at top of normal range, avoiding hyperthyroidism and increasing to 37.5 micrograms (25 and 50 alternate days) if needed. For very small and preterm infants start with 100 micrograms/m^2 daily or 10 micrograms /kg daily.

Hypothyroidism in children

Full replacement dose of thyroxine is 100 micrograms /m^2. Give a lower dose initially and change by monitoring the TSH and free T4 . Same dose for central hypothyroidism but remember the TSH will not rise.

Steroid hormone replacement

The dose needed for steroid replacement in adrenal failure or hypopituitarism is lower than that given for congenital adrenal hyperplasia- in CAH treatment must suppress ACTH secretion as well as replacing mineralocorticoid and glucocorticoid action. These treatments

* cyproterone acetate can have significant side effects of tiredness or adrenal suppression

should be given as crushed tablets since elixirs are never stable- children started on elixir elsewhere must be changed back.

Steroid replacement in adrenal failure or hypopituitarism
Hydrocortisone 15-20mg/m^2 daily
Give tds in babies and change to twice daily dose at 12 to 18 months (approximately 2/3 in the morning and 1/3 at night).

Steroid replacement in CAH
Hydrocortisone 20-25mg/m^2 daily
Starting dose for a newborn, 2.5mg tds (Corlan pellets).
Give tds in babies and change to twice daily dose at 12 to 18 months (approximately 2/3 in the morning and 1/3 at night). When growth has stopped the hydrocortisone can be changed to dexamethasone once daily.

Mineralocorticoid replacement
9α fludrocortisone 125-150 micrograms /m^2 daily
Mineralocorticoid replacement can be stopped if the child is on high dose iv hydrocortisone (for example for surgery).

Babies with salt losing should receive salt supplements (2mmol/kg/day) until they are on mixed feeding- also consider this for visits to hot countries.

Rickets
I prefer colecalciferol (Vitamin D3) or ergocalciferol (Vitamin D2) over alfacalcidol. The reason for this is that this is more physiological and much less likely to cause hypercalcaemia (because of regulation of conversion by PTH), and also that it is easier to tell if there is a metabolic defect. This is not evidence based but most paediatric endocrinologists have the same policy.

Pharmacy stock liquid colecalciferol (previously called calciferol). Doses given in Guy's formulary are for ergocalciferol and are interchangeable.

Growth hormone
Doses as in BNF:
GH deficiency 0.7-1 mg/m^2/day
Turner syndrome 1.4 mg/m^2/day
Prader Willi syndrome 1 mg/m^2/day

APPENDIX 2

Drug doses for endocrine tests

Oral glucose tolerance test
1.75 g/kg glucose to a maximum of 75 g.

Synacthen test
There are several different doses of synacthen (tetracosactride) used for the synacthen (tetracosactride)test – the differences are largely irrelevant since the dose is so large compared to endogenous ACTH secretion.
For neonates and preterm infants dose by weight is 36 micrograms/kg
Under 6 months: 62.5 micrograms
6-24 months: 125 micrograms
Over 24 months: 250 micrograms

Gonadotrophin releasing hormone (GnRH) test (gonadorelin or LHRH test)
Gonadorelin (GnRH) 2.5 micrograms /kg to a maximum of 100 micrograms as an iv bolus.

Human chorionic gonadotrophin (HCG) test
Dose (im)
under 1 year 500 units
1-10 years 1000 units
over 10 years 1500 units

Glucagon test
This carries a risk of hypoglycaemia- only Nicola Bridges to initiate this test.
Dose of glucagon 100 micrograms /kg to a maximum of 1mg given im.
Patients on steroid replacement or at risk of adrenal insufficiency must be given 50-100mg iv hydrocortisone at the end of the test.

Thyrotropin releasing hormone (TRH) or protirelin test
7 micrograms /kg protirelin (TRH) iv to a maximum of 200 micrograms.

Water deprivation test
DDAVP should only be given if the child has failed to concentrate their urine during the test, not as a routine. DDAVP runs the risk of water overload.
DDAVP (desmopressin) im dose:
Under 2 years old- 0.1 micrograms
2-8 years- 0.2 micrograms
8-14 years 0.3 micrograms
over 14 years 0.4 micrograms

Desmopressin (DDAVP) can be given nasally, as intranasal solution or as metered dose spray. The dose needed is different (much larger) and must be discussed in advance.

APPENDIX 3

Steroid cover and steroid dose adjustment for illness and surgery

The following groups may need steroid cover or dose adjustment for illness and surgery:

- Those on replacement steroids (eg adrenal insufficiency, CAH, hypopituitarism)
- Those on therapeutic steroids (eg inflammatory bowel disease, post transplant, etc)
- Anyone who has had high dose steroids in the past 6 months

Adjustment of oral steroid dose for minor illness

Children on replacement steroids (eg adrenal insufficiency, CAH, hypopituitarism) must increase their oral steroid dose if they are unwell. I normally suggest that they do not need to increase for a runny nose if the child is otherwise completely well, but for any illness more significant than this, or any fever.

Hydrocortisone dose should be increased when they are unwell. I suggest to parents 3 times the dose for 3 days. You do not need to change the fludrocortisone dose.

If the child is vomiting, not able to take oral therapy or seems to be deteriorating admit and give intravenous therapy as below.

Surgery and severe illness
It is said that 3-10 times the replacement dose of steroid is needed to cover stress. Dose should be adjusted to the circumstances, giving higher doses if the child is very sick.

Give a a single dose of iv hydrocortisone at anaesthetic induction or on admission:

under 10kg- 25mg
10-30kg-50mg
over 30kg-100mg

Continue with at least 4 times the normal replacement dose of hydrocortisone given iv as 8 hourly dose- the length of treatment will vary depending on the operation or illness.

Salt losing crisis in congenital adrenal hyperplasia

These infants need fluid replacement, steroid treatment and correction of sodium deficit.

Overleaf- letter for parents of children on steroid replacement

PAEDIATRIC ENDOCRINE CLINIC

telephone	020 8746 8687
secretary	020 8746 8885
fax	020 8746 8644

n.bridges@ic.ac.uk

17 March 2003

To whom it may concern

Patient name and details

The above patient is under the care of the paediatric endocrine clinic at Chelsea and Westminster Hospital, and is taking steroid replacement therapy.

This treatment must be given as crushed tablets and must not be omitted under any circumstances.

If the child is unwell and able to tolerate oral intake, the dose of hydrocortisone must be increased, giving three times the normal dose of steroids for three days. The increased dose should be continued if the child is still unwell after three days. The child should return to their normal dose of steroids after this. The dose of fludrocortisone should not be changed.

If the child is unwell and vomiting or not able to tolerate oral intake they must be admitted and treated with intravenous hydrocortisone.

Yours sincerely,

Dr Nicola Bridges